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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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26161	7590	11/18/2004	EXAMINER	
FISH & RICHARDSON PC 225 FRANKLIN ST BOSTON, MA 02110			PAK, YONG D	
			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 11/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/081,408

Applicant(s)

ABRAHMSSEN ET AL.

Examiner

Yong D Pak

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 August 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,4 and 7-24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,4 and 7-24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 24, 2004, amending claims 1 and 4 and canceling claims 2-3, 5-6 and 25-26, has been entered.

Claims 1, 4 and 7-24 are pending and are under consideration.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Response to Arguments

Applicant's arguments with respect to claims 1, 4 and 7-13, 15 and 17-24 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 8 is drawn to a polynucleotide encoding a fusion protein comprising a functionally equivalent variant of a glutathione S-transferase (GST). Therefore, these claims are drawn to a genus of polynucleotides encoding polypeptides having any structure. The specification only teaches one species, the polynucleotide encoding a fusion protein having GST. One species is not enough to describe the whole genus and there is no evidence on the record of the relationship between the structure of the polynucleotide encoding GST and the structure of a polynucleotide encoding a variant of GST. The specification also does not describe which residues of a GST are needed to impart the variant with GST activity. Therefore, the specification fails to describe a representative species of the genus of polynucleotides encoding a variant of GST having GST activity.

Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claim 8.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

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Claim 8 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide encoding a fusion protein comprising a GST, does not reasonably provide enablement for a polynucleotide encoding a fusion protein comprising of variants of a GST. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claim 8 is drawn to a polynucleotide encoding a fusion protein comprising a functionally equivalent variant of a glutathione S-transferase (GST). Therefore, claim 8 encompasses polynucleotides encoding a fusion protein comprising any variants of a GST. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides encoding GST variants, broadly encompassed by the claims. Since the amino acid sequence of the encoded protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids

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in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a polynucleotide encoding a fusion protein comprising of a GST. It would require undue experimentation of the skilled artisan to make and use the claimed variants. The specification is limited to teaching the use of a polynucleotide encoding a GST but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polynucleotides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polynucleotides encompassed by this claim.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

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The specification does not support the broad scope of the claims which encompass all modifications and fragments of polynucleotides encoding any GST, including variants and mutants, because the specification does not establish: (A) regions of the protein structure which may be modified without affecting GST activity; (B) the general tolerance of GST to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polynucleotides encoding GST variants and mutants. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of GST variants having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and claims 7-24 depending therefrom is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, it is not clear if the fusion protein consists of the peptides/polypeptides of (i)-(v) in the order as listed in the claim or if the fusion protein can consists of the parts (i)-(v) in any order. As applicants have not provided any particular order of peptides/polypeptides of (i)-(v), Examiner has interpreted the claims broadly to mean that the fusion protein can consist of the peptides/polypeptides of (i)-(v) in any order.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 depends from claim 2, which has been canceled. Therefore, the claim has not been considered under other statutes.

Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 recites the phrase "derivative thereof". The metes and bounds of this phrase is not clear to the Examiner. Literally, the term "derivative" means a substance that can be made from another substance. Therefore, it is not clear to the Examiner either from the specification or from the claims as to what applicants mean by the above

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phrase. As applicants have not provided a definition for the above phrase, Examiner has interpreted the claims broadly to mean that a "derivative thereof" of a glutathione encompasses molecules which are variants or mutants of a glutathione.

Claims 22-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 22-23, the phrase "fused to a fusion partner resulting in a fusion protease" is confusing. It is not clear if the protease is fused to the fusion partner of the fusion protein recited in claim 1 or is fused to a separate fusion partner, resulting in a protease fusion independent from the fusion protein recited in claim 1 (of which claims 22-23 ultimately depend from). Further, the claims ultimately depend from claim 1 and claim 1 is drawn to a fusion protein consisting of only a signal peptide, fusion partner, SSAO, a protease cleavage site and spacers. Claim 1 recites the phrase "consisting of", rendering the claim with a closed language, additional amino acid sequences not recited in claim 1, such as the protease, cannot be added to the fusion protein. Therefore, the claims are indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 7, 8-10, 15, 17-19 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al., Huston et al. and Tudyka et al.

Claims 1, 7-10 are drawn to a polynucleotide encoding a fusion protein consisting of a signal peptide, a semicarbazide-sensitive amine oxidase (SSAO) consisting of amino acids 29-763 of SEQ ID NO:2 or an enzymatically active fragment thereof, a fusion partner comprising the amino acid sequence of SEQ ID NO:4 or SEQ ID NO:5, a protease cleavage site and one or more spacer amino acid sequences. Claim 15 is drawn to a vector comprising a polynucleotide encoding said fusion protein and claims 17-19 and 24 are drawn to methods of purifying the fusion protein and SSAO.

Smith et al. (form PTO-1449 – reference AYY) teach an amino oxidase that is 100% identical to the semicarbazide-sensitive amino oxidase (SSAO) of SEQ ID NO:2 of the instant invention (Figure 1, page 20 and SwissProt sequence alignment). Smith et al. teach that the transmembrane domain is between residues 5-27 (Figure 1, page 20 and page 21). Art and the specification teach that the soluble form of SSAO lacks the membrane spanning portion of the wild-type SSAO. Even though Smith et al. teaches the transmembrane domain as including residues 5-27 of SEQ ID NO:27, one of ordinary skill in the art would have also recognized the advantage of using amino acids 29 to 763 of SEQ ID NO:2. The amino acid at position 28 is an Arg. There are numerous proteases in the cell and growth medium that cleaves at arginine residues (Huston et al. – U.S. Patent 5,013,653, Column 10, Table 1). To ensure that the fusion partner and SSAO are not cleaved prematurely, it would have been obvious to fuse the protease cleavage site to a SSAO consisting of amino acids 29-763 of SEQ ID NO:2.

The difference between the reference of Smith et al. and the instant invention is that the reference of Smith et al. does not teach a polynucleotide encoding a secreted fusion protein comprising a signal peptide, a fusion partner, a protease cleavage site and at least one spacer amino acid sequence nor a vector comprising said polynucleotide nor a method of purifying said fusion protein and SSAO.

Huston et al. (U.S. Patent No. 5,013,653 – cited on previous form PTO-892) teach polynucleotide encoding a fusion protein comprising a signal peptide, a target protein and a protease cleavage site between the fusion partner and to the target protein (Column 1). Huston et al. teach that a signal peptide can be used for secretion

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of the fusion protein and in order protect the target protein from intracellular degradation during expression or isolation/purification(Column 1). Huston et al. also teach that a protease cleavage site can be incorporated between the target protein and any additional fused material (column 1 and 2). Huston et al. also teach a vector comprising said polynucleotide, a method of producing the target protein and a method of immobilizing the fused target protein (Column 2 and Examples 1-4).

Tudyka et al. (form PTO-1449 – Reference ACCC) teach that GST can be used as a fusion partner that enables dimerization of a target recombinant protein and confer enzymatic reporter activity (abstract and page 2180). Tudyka et al. teach that glutathione S-transferase (GST) from *Schistosoma* that is 100% identical to the GST of SEQ ID NO:4 of the instant invention. Tudyka et al. teach that replacing three of the four exposed cysteine residues in GST (residues 85, 138 and 178) prevents misfolding due to incorrect disulfide bonds (abstract, Figure 2-B, page 2182 and 2185) and the resulting GST mutant is 100% identical to SEQ ID NO:5 of the instant invention. Tudyka et al. also teach that the fusion protein was purified by means of an affinity column with glutathione (abstract) and the GST protein can be proteolytically removed after the fusion protein is produced in the cytoplasm (page 2185).

Therefore, combining the teaches of the above references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make a polynucleotide encoding a fusion protein comprising a signal peptide, a fusion partner of Tudyka et al., a soluble form of SSAO of Smith et al., and a protease cleavage site between the fusion partner and to the target protein, as outlined by

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Huston et al. The motivation of making the fusion construct is to facilitate the secretion, isolation and purification of a soluble SSAO. The motivation of truncating the transmembrane domain of SSAO is to produce soluble SSAO, thereby increasing the efficiency of the purification process. The motivation of using amino acids 29-763 of SEQ ID NO:2 is to lower the risk of the target protein from being cleaved prematurely by proteases in the cell or cell culture. The motivation of using the fusion partner of Tudyka et al. is to enable dimerization of SSAO and confer enzymatic reporter activity. The motivation of using the mutant GST of Tudyka et al. is to prevent misfolding of the protein. One of ordinary skill in the art would have had a reasonable expectation of success of making a polynucleotide encoding a fusion protein since the individual proteins incorporated into the fusion proteins are well known in the art and Huston et al. and Tudyka et al. in combination teach detailed steps in making a successful fusion protein and methods of purifying the fusion protein and ultimately the protein of interest.

Therefore, the above references render claims 1, 7, 8-10, 15, 17-19 and 24 prima facie obvious to one of ordinary skill in the art.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al., Huston et al. and Tudyka et al. and Zambidis et al.

Claim 11 is drawn to a polynucleotide encoding a fusion protein consisting of a mouse IgG1 heavy chain signal peptide, a semicarbazide-sensitive amine oxidase

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(SSAO) consisting of amino acids 29-763 of SEQ ID NO:2, a fusion partner, a protease cleavage site and one or more spacer amino acid sequences.

Smith et al., Huston et al. and Tudyka et al., in combination teach a polynucleotide encoding a fusion protein consisting of a signal peptide, a semicarbazide-sensitive amine oxidase (SSAO) consisting of amino acids 29-763 of SEQ ID NO:2, a fusion partner comprising the amino acid sequence of SEQ ID NO:4 or SEQ ID NO:5, a protease cleavage site and one or more spacer amino acid sequences and a method of purifying the fusion protein, as discussed above.

The difference between the references of Smith et al., Huston et al. and Tudyka et al. is that the combined references do not teach a polynucleotide encoding a fusion protein having a mouse IgG1 heavy chain signal peptide. Huston et al. only teaches using a human IgG1 as a signal peptide in the fusion protein.

Zambidis et al. (cited on previous form PTO-892) teach a mouse IgG1 heavy chain, used as a signal peptide in a fusion protein (abstract).

Therefore, combining the teaches of the above references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make a polynucleotide encoding a fusion protein comprising a mouse IgG1 signal peptide. The motivation of making such a fusion construct is to facilitate the expression, secretion and purification of the target protein. One of ordinary skill in the art would have had a reasonable expectation of success since IgG1 or other immunoglobulin proteins are well known and well practiced in the art in facilitating expression and secretion of heterologous proteins.

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Therefore, the above references render claim 11 prima facie obvious to one of ordinary skill in the art.

Claims 12-13 and 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al., Huston et al. and Tudyka et al. and Brenda Enzyme Database.

Claims 12-13 and 20-21 are drawn to a polynucleotide encoding a fusion protein consisting of a signal peptide, a semicarbazide-sensitive amine oxidase (SSAO) consisting of amino acids 29-763 of SEQ ID NO:2, a fusion partner, a protease cleavage site comprising the amino acid sequence of SEQ ID NO:6 and one or more spacer amino acid sequences and a method of purifying the fusion protein.

Smith et al., Huston et al. and Tudyka et al., in combination teach a polynucleotide encoding a fusion protein consisting of a signal peptide, a semicarbazide-sensitive amine oxidase (SSAO) consisting of amino acids 29-763 of SEQ ID NO:2, a fusion partner comprising the amino acid sequence of SEQ ID NO:4 or SEQ ID NO:5, a protease cleavage site and one or more spacer amino acid sequences and a method of purifying the fusion protein, as discussed above.

The difference between the references of Smith et al., Huston et al. and Tudyka et al. is that the combined references do not teach a polynucleotide encoding a fusion protein having a protease cleavage site comprising the amino acid sequence of SEQ ID NO:6.

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Huston et al. teaches that many different protease cleavage sites can be introduced into the fusion protein (Columns 9-11). Brenda Enzyme Database (EC 3.4.22.28 – form PTO-892) teach a 3C protease from Coxsackievirus that is 100% identical to SEQ ID NO:6 of the instant invention. The Database also teaches a picornvirus 3C protease and a rhinovirus 3C protease (pages 3-4). There are many types of protease cleavage sites and 3C proteases is one of the many enzymes capable of safely cleaving a fusion partner from the target protein.

Therefore, combining the teaches of the above references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make a polynucleotide encoding a fusion protein comprising any of the 3C proteases listed in the Brenda Enzyme Database. The motivation of incorporating a cleavage site between the SSAO and GST is to cleave off the GST protein after the fusion protein is produced in the cytoplasm. One of ordinary skill in the art would have had a reasonable expectation of success since 3C proteases are well known and have been widely used in cleavage sites between target proteins and additional fused material.

Therefore, the above references render claims 12-13 and 20-21 prima facie obvious to one of ordinary skill in the art.

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935.


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The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner


Ponnathapu Achutamurthy
Patent Examiner
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